Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of SUN13837 Injection in Adult Subjects with Acute Spinal Cord Injury

Summary

EudraCT number	2012-004373-80
Trial protocol	GB CZ ES PL
Global end of trial date	21 March 2015

Results information

Result version number	v1 (current)
This version publication date	31 July 2016
First version publication date	31 July 2016

Trial information

Trial identification

Sponsor protocol code	ASBI603

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01502631
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 105,377

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc
Sponsor organisation address	399 Thornall St., Edison, New Jersey, United States, 08837
Public contact	Clinical Trials Information, Asubio Pharmaceuticals, Inc., +001 201368 5020, info@asubio.com
Scientific contact	Clinical Trials Information, Asubio Pharmaceuticals, Inc., +001 201368 5020, info@asubio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to determine if treatment of acute spinal cord injury (ASCI) with SUN13837, when compared with placebo, resulted in a greater improvement in measures of overall functional independence by a comparison of the difference in the final mean total Spinal Cord Independence Measure, version III (SCIM III) scores between the 2 treatment groups.

Protection of trial subjects:

The safety assessments included adverse events, vital signs, electrocardiograms (ECGs), physical examination and clinical laboratory tests.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	United States: 53
Worldwide total number of subjects	61
EEA total number of subjects	8

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	57
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 69 subjects screened. Of which 65 subjects were randomized. 4 subjects were randomized but not treated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	SUN13837

Arm description:

Subjects received SUN13837 1 milligram per kilogram (mg/kg) intravenous injection once daily for 28 days.

Arm type	Experimental
Investigational medicinal product name	SUN13837
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received SUN13837 1 milligram per kilogram (mg/kg) intravenous injection once daily for 28 days.

Arm title	Placebo

Arm description:

Subjects received placebo intravenous injection once daily for 28 days.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received placebo intravenous injection once daily for 28 days.

Number of subjects in period 1	SUN13837	Placebo
Started	30	31
Completed	16	18
Not completed	14	13
Adverse event, serious fatal	2	3
Early withdrawal from study treatment	6	5
Consent withdrawn by subject	-	1
Subject Non-Compliant	1	-
Unspecified	3	2
Lost to follow-up	2	2

Baseline characteristics

Reporting groups	
Reporting group title	SUN13837
Reporting group description:	
Subjects received SUN13837 1 milligram per kilogram (mg/kg) intravenous injection once daily for 28 days.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo intravenous injection once daily for 28 days.	

Reporting group values	SUN13837	Placebo	Total
Number of subjects	30	31	61
Age categorical			
Units: Subjects			
Adults (18-64 years)	28	29	57
From 65-84 years	2	2	4
Age continuous			
Units: years			
arithmetic mean	37.9	38.8	
standard deviation	± 16.58	± 17.22	-
Gender categorical			
Units: Subjects			
Female	4	5	9
Male	26	26	52

End points

End points reporting groups	
Reporting group title	SUN13837
Reporting group description:	
Subjects received SUN13837 1 milligram per kilogram (mg/kg) intravenous injection once daily for 28 days.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo intravenous injection once daily for 28 days.	

Primary: Spinal Cord Independence Measure, version III (SCIM III) Total Score at Week 16

End point title	Spinal Cord Independence Measure, version III (SCIM III) Total Score at Week 16
End point description:	
The SCIM III is a comprehensive rating scale that measures the ability of subjects with spinal cord injury to perform everyday tasks. The SCIM III has 19 items that assess 3 domains: Self-Care (6 items, scores range from 0 to 20), Respiration and Sphincter Management (4 items, scores range from 0 to 40), and Mobility (9 items, scores range from 0 to 40). The total SCIM score ranges from 0 to 100. Higher value represents increase in the improvement. The Intent-to-Treat population included all randomized subjects who received at least 7 doses of study drug and had at least 1 SCIM III evaluation.	
End point type	Primary
End point timeframe:	
Week 16	

End point values	SUN13837	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: units on a scale				
least squares mean (standard error)	38.14 (± 4.74)	33.6 (± 4.703)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	SUN13837 v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4912
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	4.54

Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.48
upper limit	15.56
Variability estimate	Standard error of the mean
Dispersion value	6.524

Secondary: Total Motor Score (TMS) of International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) at Week 16

End point title	Total Motor Score (TMS) of International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) at Week 16

End point description:

The TMS was the sum of the overall Upper Extremity Motor Score (UEMS) and the overall Lower Extremity Motor Score (LEMS) of ISNCSCI. The Upper Extremity Motor Score (UEMS) was defined as the sum of the motor function scores (based on the 0 to 5-point scale). A separate sum was obtained for the right and left sides (a maximum of 25 points each) and for an overall score (with a maximum score of 50). The Lower Extremity Motor Score (LEMS) was defined as the sum of the motor function scores. A separate sum was obtained for the right and left sides (a maximum of 25 points each) and for an overall score (with a maximum score of 50). Therefore, the maximum TMS score was 100. The TMS score reaches a maximum of 100 points in an individual with a fully functional spinal cord. The Intent-to-Treat population included all randomized subjects who received at least 7 doses of study drug and had at least 1 SCIM III evaluation.

End point type	Secondary

End point timeframe:

Week 16

End point values	SUN13837	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: units on a scale				
least squares mean (standard error)	16.58 (± 4.277)	14.07 (± 4.175)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v SUN13837
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6719
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	2.51

Confidence interval	
level	90 %
sides	2-sided
lower limit	-7.37
upper limit	12.38
Variability estimate	Standard error of the mean
Dispersion value	5.874

Secondary: Self-Care and Mobility Subscale Scores of Spinal Cord Independence Measure, version III (SCIM III) at Week 16

End point title	Self-Care and Mobility Subscale Scores of Spinal Cord Independence Measure, version III (SCIM III) at Week 16

End point description:

The SCIM III is a comprehensive rating scale that measures the ability of subjects with spinal cord injury to perform everyday tasks. The SCIM III has 19 items that assess 3 domains: Self-Care (6 items, scores range from 0 to 20), Respiration and Sphincter Management (4 items, scores range from 0 to 40), and Mobility (9 items, scores range from 0 to 40). The total SCIM score ranges from 0 to 100. SCIM III Self-Care subscale offered a means to evaluate upper extremity activities. Higher value represents increase in the improvement. The Intent-to-Treat population included all randomized subjects who received at least 7 doses of study drug and had at least 1 SCIM III evaluation.

End point type	Secondary

End point timeframe:

Week 16

End point values	SUN13837	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: units on a scale				
least squares mean (standard error)	18.73 (± 3.124)	15.02 (± 3.101)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	SUN13837 v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3951
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	3.71

Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.59
upper limit	11.01
Variability estimate	Standard error of the mean
Dispersion value	4.298

Secondary: Number of Subjects With American Spinal Injury Association Impairment Scale (AIS) Grade - Improvement from Baseline at Final Assessment at Week 16

End point title	Number of Subjects With American Spinal Injury Association Impairment Scale (AIS) Grade - Improvement from Baseline at Final Assessment at Week 16

End point description:

Subjects were assessed for AIS based on the following grading scheme: A (complete, no motor or sensory function is preserved in the sacral levels 4 through 5), B (incomplete, sensory but no motor function is preserved below the neurological level and includes sacral levels 4 through 5), C (incomplete, motor function is preserved below the neurological level and more than half of the key muscles below the neurological level have a muscle grade of less than 3), D (incomplete, motor function preserved below the neurological level and at least half of the key muscles below the neurological level have a muscle grade of 5 or more) and E (normal). Improvement was defined as 1 or more shift toward AIS grade (B-E) from baseline. The Intent-to-Treat population included all randomized subjects who received at least 7 doses of study drug and had at least 1 SCIM III evaluation. Here, "N" is number of subjects analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	SUN13837	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: subjects	12	15		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	SUN13837 v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4916
Method	ANCOVA
Parameter estimate	Odds ratio (OR)
Point estimate	0.67

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.26
upper limit	1.73

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From First Administration of Study Drug up to End of Study (Day 182)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	SUN13837
Reporting group description:	
Subjects received SUN13837 1 milligram per kilogram (mg/kg) intravenous injection once daily for 28 days.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo intravenous injection once daily for 28 days.	

Serious adverse events	SUN13837	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 30 (36.67%)	17 / 31 (54.84%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Multiple myeloma			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Withdrawal of life support			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Euthanasia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	3 / 30 (10.00%)	3 / 31 (9.68%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 30 (10.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			

subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	2 / 30 (6.67%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			

subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyuria			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine abnormality			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroiditis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	3 / 30 (10.00%)	3 / 31 (9.68%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 30 (10.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection pseudomonal			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection fungal			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	SUN13837	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 30 (100.00%)	31 / 31 (100.00%)	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	9 / 30 (30.00%)	8 / 31 (25.81%)	
occurrences (all)	9	8	
Hypotension			
subjects affected / exposed	5 / 30 (16.67%)	6 / 31 (19.35%)	
occurrences (all)	5	6	
Deep vein thrombosis			
subjects affected / exposed	2 / 30 (6.67%)	5 / 31 (16.13%)	
occurrences (all)	2	5	
Hypertension			
subjects affected / exposed	1 / 30 (3.33%)	5 / 31 (16.13%)	
occurrences (all)	1	9	
Flushing			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Neurogenic shock			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Phlebitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Phlebitis superficial			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Venous thrombosis limb			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	2	0	

Surgical and medical procedures			
Osteosynthesis			
subjects affected / exposed	0 / 30 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Sinus operation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	17 / 30 (56.67%)	14 / 31 (45.16%)	
occurrences (all)	26	18	
Oedema peripheral			
subjects affected / exposed	5 / 30 (16.67%)	4 / 31 (12.90%)	
occurrences (all)	5	4	
Pain			
subjects affected / exposed	2 / 30 (6.67%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Chest pain			
subjects affected / exposed	1 / 30 (3.33%)	2 / 31 (6.45%)	
occurrences (all)	1	4	
Catheter site inflammation			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Generalised oedema			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Medical device pain			
subjects affected / exposed	0 / 30 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Oedema			
subjects affected / exposed	0 / 30 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Chest discomfort			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Chills			

subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Hyperthermia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	3	
Impaired healing			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Implant site erosion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Irritability			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Temperature regulation disorder			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	2 / 30 (6.67%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Penis disorder			
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Cervix oedema			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Epididymitis			

subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Genital burning sensation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Pelvic pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Scrotal oedema			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Vaginal discharge			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	8 / 30 (26.67%)	4 / 31 (12.90%)	
occurrences (all)	8	4	
Atelectasis			
subjects affected / exposed	5 / 30 (16.67%)	6 / 31 (19.35%)	
occurrences (all)	5	7	
Oropharyngeal pain			
subjects affected / exposed	5 / 30 (16.67%)	6 / 31 (19.35%)	
occurrences (all)	5	7	
Respiratory failure			
subjects affected / exposed	6 / 30 (20.00%)	4 / 31 (12.90%)	
occurrences (all)	6	6	
Pleural effusion			
subjects affected / exposed	6 / 30 (20.00%)	1 / 31 (3.23%)	
occurrences (all)	6	1	
Pneumonia aspiration			
subjects affected / exposed	3 / 30 (10.00%)	3 / 31 (9.68%)	
occurrences (all)	3	3	
Dyspnoea			

subjects affected / exposed	1 / 30 (3.33%)	4 / 31 (12.90%)	
occurrences (all)	2	5	
Increased bronchial secretion			
subjects affected / exposed	2 / 30 (6.67%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Pulmonary oedema			
subjects affected / exposed	2 / 30 (6.67%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Respiratory distress			
subjects affected / exposed	2 / 30 (6.67%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Cough			
subjects affected / exposed	1 / 30 (3.33%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Hypoxia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Nasal dryness			
subjects affected / exposed	1 / 30 (3.33%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Aspiration			
subjects affected / exposed	0 / 30 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Bronchial secretion retention			
subjects affected / exposed	0 / 30 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Lung infiltration			
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Tachypnoea			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Acute respiratory failure			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Apnoea			

subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Bronchospasm			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Choking			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Diaphragmatic paralysis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Haemoptysis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Hypoventilation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Pneumothorax			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Pulmonary congestion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Pulmonary embolism			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Respiratory acidosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Respiratory depression			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Respiratory depth decreased			

subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Sinus congestion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Tracheal oedema			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 30 (46.67%)	12 / 31 (38.71%)	
occurrences (all)	17	13	
Anxiety			
subjects affected / exposed	9 / 30 (30.00%)	10 / 31 (32.26%)	
occurrences (all)	9	13	
Depression			
subjects affected / exposed	8 / 30 (26.67%)	9 / 31 (29.03%)	
occurrences (all)	9	9	
Agitation			
subjects affected / exposed	5 / 30 (16.67%)	1 / 31 (3.23%)	
occurrences (all)	5	2	
Confusional state			
subjects affected / exposed	2 / 30 (6.67%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Delirium			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Adjustment disorder			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	

Claustrophobia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Delirium tremens			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Depressed mood			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Hallucination			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Mental status changes			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Nightmare			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Personality disorder			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Psychotic disorder			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	7 / 30 (23.33%)	5 / 31 (16.13%)	
occurrences (all)	7	5	
Gamma-glutamyltransferase increased			

subjects affected / exposed	5 / 30 (16.67%)	3 / 31 (9.68%)		
occurrences (all)	5	3		
Blood lactate dehydrogenase increased				
subjects affected / exposed	3 / 30 (10.00%)	3 / 31 (9.68%)		
occurrences (all)	5	4		
Aspartate aminotransferase increased				
subjects affected / exposed	2 / 30 (6.67%)	3 / 31 (9.68%)		
occurrences (all)	2	3		
Alanine aminotransferase increased				
subjects affected / exposed	1 / 30 (3.33%)	3 / 31 (9.68%)		
occurrences (all)	1	3		
Haematocrit decreased				
subjects affected / exposed	4 / 30 (13.33%)	0 / 31 (0.00%)		
occurrences (all)	4	0		
Haemoglobin decreased				
subjects affected / exposed	4 / 30 (13.33%)	0 / 31 (0.00%)		
occurrences (all)	4	0		
Hepatic enzyme increased				
subjects affected / exposed	2 / 30 (6.67%)	2 / 31 (6.45%)		
occurrences (all)	2	2		
Blood alkaline phosphatase increased				
subjects affected / exposed	2 / 30 (6.67%)	1 / 31 (3.23%)		
occurrences (all)	2	1		
Platelet count decreased				
subjects affected / exposed	2 / 30 (6.67%)	1 / 31 (3.23%)		
occurrences (all)	2	1		
Blood creatine increased				
subjects affected / exposed	0 / 30 (0.00%)	2 / 31 (6.45%)		
occurrences (all)	0	2		
Blood glucose increased				
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)		
occurrences (all)	1	1		
Body temperature increased				

subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)		
occurrences (all)	2	0		
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)		
occurrences (all)	1	1		
International normalised ratio increased				
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)		
occurrences (all)	2	0		
Neutrophil count increased				
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)		
occurrences (all)	4	0		
Red blood cell count decreased				
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)		
occurrences (all)	2	0		
White blood cell count increased				
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)		
occurrences (all)	2	0		
Activated partial thromboplastin time prolonged				
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Bacterial test				
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Blood albumin decreased				
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Blood bicarbonate increased				
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Blood chloride decreased				
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Blood magnesium decreased				

subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Blood sodium decreased				
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)		
occurrences (all)	0	1		
Blood urea increased				
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Body temperature decreased				
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
C-reactive protein increased				
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Chest X-ray abnormal				
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Electrocardiogram ST segment elevation				
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)		
occurrences (all)	0	1		
Electrocardiogram abnormal				
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Haemophilus test positive				
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Heart rate decreased				
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)		
occurrences (all)	0	1		
Mean arterial pressure decreased				
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)		
occurrences (all)	0	1		
Myelocyte count increased				
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)		
occurrences (all)	1	0		

Oxygen consumption increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Oxygen saturation decreased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Platelet count increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Prothrombin time prolonged			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
White blood cell count decreased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
White blood cells urine positive			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	4 / 30 (13.33%)	2 / 31 (6.45%)	
occurrences (all)	6	2	
Autonomic dysreflexia			
subjects affected / exposed	2 / 30 (6.67%)	3 / 31 (9.68%)	
occurrences (all)	2	3	
Procedural pain			
subjects affected / exposed	3 / 30 (10.00%)	1 / 31 (3.23%)	
occurrences (all)	3	1	
Procedural site reaction			
subjects affected / exposed	1 / 30 (3.33%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Muscle strain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Post procedural haemorrhage			

subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Wound			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Clavicle fracture			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Epicondylitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Incision site oedema			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Joint dislocation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Open wound			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	2	
Penis injury			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Post procedural oedema			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Postoperative wound complication			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Procedural haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Pseudomeningocele			

subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Spinal column injury			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Wound dehiscence			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Wound necrosis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	5 / 30 (16.67%)	4 / 31 (12.90%)	
occurrences (all)	5	5	
Tachycardia			
subjects affected / exposed	8 / 30 (26.67%)	1 / 31 (3.23%)	
occurrences (all)	8	1	
Atrial fibrillation			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Cardiac failure congestive			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Supraventricular tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Ventricular extrasystoles			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	

Nervous system disorders			
Muscle spasticity			
subjects affected / exposed	12 / 30 (40.00%)	9 / 31 (29.03%)	
occurrences (all)	13	11	
Neuralgia			
subjects affected / exposed	13 / 30 (43.33%)	8 / 31 (25.81%)	
occurrences (all)	13	9	
Headache			
subjects affected / exposed	9 / 30 (30.00%)	4 / 31 (12.90%)	
occurrences (all)	10	5	
Dizziness			
subjects affected / exposed	3 / 30 (10.00%)	1 / 31 (3.23%)	
occurrences (all)	3	1	
Dysaesthesia			
subjects affected / exposed	3 / 30 (10.00%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Hypertonia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Hypoaesthesia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Sedation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Spinal cord compression			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Spinal cord oedema			

subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	8 / 30 (26.67%)	10 / 31 (32.26%)	
occurrences (all)	8	13	
Anaemia			
subjects affected / exposed	5 / 30 (16.67%)	11 / 31 (35.48%)	
occurrences (all)	6	11	
Haemorrhagic anaemia			
subjects affected / exposed	2 / 30 (6.67%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Thrombocytopenia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Thrombocytosis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Bandaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Blood disorder			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	2	
Eosinophilia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Nucleated red cells			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	

Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Ear pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Eye disorders			
Dry eye			
subjects affected / exposed	5 / 30 (16.67%)	3 / 31 (9.68%)	
occurrences (all)	5	3	
Diplopia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	12 / 30 (40.00%)	10 / 31 (32.26%)	
occurrences (all)	15	14	
Constipation			
subjects affected / exposed	7 / 30 (23.33%)	11 / 31 (35.48%)	
occurrences (all)	12	17	
Diarrhoea			
subjects affected / exposed	6 / 30 (20.00%)	5 / 31 (16.13%)	
occurrences (all)	7	6	
Vomiting			
subjects affected / exposed	5 / 30 (16.67%)	6 / 31 (19.35%)	
occurrences (all)	7	6	
Dysphagia			
subjects affected / exposed	5 / 30 (16.67%)	5 / 31 (16.13%)	
occurrences (all)	5	6	
Ileus			
subjects affected / exposed	6 / 30 (20.00%)	4 / 31 (12.90%)	
occurrences (all)	6	4	
Neurogenic bowel			

subjects affected / exposed	4 / 30 (13.33%)	4 / 31 (12.90%)	
occurrences (all)	4	4	
Haemorrhoids			
subjects affected / exposed	5 / 30 (16.67%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Dry mouth			
subjects affected / exposed	3 / 30 (10.00%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Dyspepsia			
subjects affected / exposed	2 / 30 (6.67%)	3 / 31 (9.68%)	
occurrences (all)	2	5	
Abdominal discomfort			
subjects affected / exposed	3 / 30 (10.00%)	1 / 31 (3.23%)	
occurrences (all)	3	1	
Abdominal distension			
subjects affected / exposed	0 / 30 (0.00%)	3 / 31 (9.68%)	
occurrences (all)	0	3	
Flatulence			
subjects affected / exposed	2 / 30 (6.67%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Abdominal pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	0 / 30 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 30 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Haematochezia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Oesophagitis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Abdominal pain lower			

subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Anal ulcer			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Anorectal discomfort			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Dental caries			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Duodenal ulcer			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Eructation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Faeces discoloured			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Frequent bowel movements			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Haematemesis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Ileus paralytic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Impaired gastric emptying			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Odynophagia			

subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Proctalgia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Reflux gastritis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Salivary hypersecretion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	13 / 30 (43.33%)	13 / 31 (41.94%)	
occurrences (all)	26	24	
Rash			
subjects affected / exposed	9 / 30 (30.00%)	4 / 31 (12.90%)	
occurrences (all)	10	4	
Pruritus			
subjects affected / exposed	3 / 30 (10.00%)	4 / 31 (12.90%)	
occurrences (all)	4	6	
Dry skin			
subjects affected / exposed	3 / 30 (10.00%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Skin ulcer			
subjects affected / exposed	1 / 30 (3.33%)	4 / 31 (12.90%)	
occurrences (all)	1	4	
Blister			
subjects affected / exposed	1 / 30 (3.33%)	2 / 31 (6.45%)	
occurrences (all)	1	3	
Skin disorder			
subjects affected / exposed	2 / 30 (6.67%)	1 / 31 (3.23%)	
occurrences (all)	3	1	

Dermatitis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Erythema			
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Dermatitis contact			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Hyperkeratosis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Pruritus allergic			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Rash pruritic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Skin maceration			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Neurogenic bladder			
subjects affected / exposed	5 / 30 (16.67%)	5 / 31 (16.13%)	
occurrences (all)	5	5	
Haematuria			
subjects affected / exposed	2 / 30 (6.67%)	3 / 31 (9.68%)	
occurrences (all)	3	3	
Urinary incontinence			
subjects affected / exposed	1 / 30 (3.33%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Urinary retention			

subjects affected / exposed	1 / 30 (3.33%)	3 / 31 (9.68%)	
occurrences (all)	1	5	
Bladder spasm			
subjects affected / exposed	2 / 30 (6.67%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Hypertonic bladder			
subjects affected / exposed	1 / 30 (3.33%)	2 / 31 (6.45%)	
occurrences (all)	1	3	
Renal failure acute			
subjects affected / exposed	0 / 30 (0.00%)	3 / 31 (9.68%)	
occurrences (all)	0	3	
Polyuria			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Automatic bladder			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Bladder discomfort			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Calculus bladder			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Dysuria			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Glycosuria			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Leukocyturia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Micturition urgency			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Renal tubular necrosis			

subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Urethral haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Urine abnormality			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 30 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Hypothyroidism			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	10 / 30 (33.33%)	7 / 31 (22.58%)	
occurrences (all)	13	7	
Muscle spasms			
subjects affected / exposed	8 / 30 (26.67%)	6 / 31 (19.35%)	
occurrences (all)	8	7	
Neck pain			
subjects affected / exposed	5 / 30 (16.67%)	4 / 31 (12.90%)	
occurrences (all)	6	5	
Pain in extremity			
subjects affected / exposed	3 / 30 (10.00%)	2 / 31 (6.45%)	
occurrences (all)	3	3	
Arthralgia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 31 (3.23%)	
occurrences (all)	3	2	
Back pain			
subjects affected / exposed	1 / 30 (3.33%)	2 / 31 (6.45%)	
occurrences (all)	1	3	
Extraskeletal ossification			

subjects affected / exposed	1 / 30 (3.33%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Periarthritis			
subjects affected / exposed	0 / 30 (0.00%)	3 / 31 (9.68%)	
occurrences (all)	0	3	
Extremity contracture			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Pain in jaw			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Tendonitis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Rhabdomyolysis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Groin pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Joint contracture			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Joint effusion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Joint range of motion decreased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Muscle contracture			

subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Myofascial pain syndrome			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Myositis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Pubic pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Torticollis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	20 / 30 (66.67%)	23 / 31 (74.19%)	
occurrences (all)	40	35	
Pneumonia			
subjects affected / exposed	7 / 30 (23.33%)	16 / 31 (51.61%)	
occurrences (all)	8	18	
Respiratory tract infection			
subjects affected / exposed	2 / 30 (6.67%)	3 / 31 (9.68%)	
occurrences (all)	2	3	
Clostridial infection			
subjects affected / exposed	1 / 30 (3.33%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Upper respiratory tract infection			
subjects affected / exposed	2 / 30 (6.67%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Candidiasis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Cystitis klebsiella			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	

Nasopharyngitis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Otitis externa			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Staphylococcal infection			
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Abdominal infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Acarodermatitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Acute sinusitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Bacterial disease carrier			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Bacteriuria			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	2	
Cellulitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	

Fungal infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Fungal skin infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis viral			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Herpes dermatitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Herpes virus infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Infected skin ulcer			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Intraspinal abscess			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Lung infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Lung infection pseudomonal			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Nail infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	

Onychomycosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Paronychia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Pneumonia bacterial			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Pneumonia streptococcal			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Post procedural infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Postoperative wound infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Purulent discharge			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Sepsis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Tracheitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	

Tracheobronchitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Tracheostomy infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	5 / 30 (16.67%)	5 / 31 (16.13%)	
occurrences (all)	5	5	
Hypokalaemia			
subjects affected / exposed	3 / 30 (10.00%)	5 / 31 (16.13%)	
occurrences (all)	5	8	
Dehydration			
subjects affected / exposed	4 / 30 (13.33%)	2 / 31 (6.45%)	
occurrences (all)	4	2	
Hyperglycaemia			
subjects affected / exposed	1 / 30 (3.33%)	5 / 31 (16.13%)	
occurrences (all)	1	5	
Hyponatraemia			
subjects affected / exposed	4 / 30 (13.33%)	2 / 31 (6.45%)	
occurrences (all)	4	2	
Hypocalcaemia			
subjects affected / exposed	3 / 30 (10.00%)	1 / 31 (3.23%)	
occurrences (all)	3	1	
Fluid overload			
subjects affected / exposed	1 / 30 (3.33%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Decreased appetite			

subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Fluid retention			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Vitamin D deficiency			
subjects affected / exposed	0 / 30 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Cachexia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Hypercalcaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Hyperchloraemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Hypernatraemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Hypomagnesaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Malnutrition			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Sodium retention			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2011	The overall reason for the amendment was to exclude subjects with renal compromise, hepatic dysfunction, and/or hepatic impairment at screening before the first dose of study drug. - Required that subjects discontinue use of potent CYP3A4/5 inducers for the first 35 days of the study (that is, for the duration of dosing plus 5.5 times the terminal elimination phase half-life of SUN13837). - Added that concomitant administration of CYP3A substrates with a narrow therapeutic index should be avoided during the first 35 days of the study; subjects requiring such therapy should be carefully monitored. - Added that exploratory pharmacokinetic (PK) analysis of 1-benzyl-N-methylpiperidin-4-amine (BMP) (ASB 15490) was conducted. - Added that if blood ethanol concentration (if measured within 72 hours of admission) and/or anatomical length of spinal cord injury was obtained by the hospital as part of patient care, these data, along with date obtained, were to be recorded in the Electronic Case Report Form (eCRF). - Amended the statistical methods section to include multiple imputation methods for handling missing data.
07 November 2012	The overall reason for the amendment was to allow the enrollment of American Spinal Injury Association Impairment Scale grade of B and C (AIS B and C) subjects which allowed for the evaluation of SUN13837 injection in a broader population of acute spinal cord injury subjects. AIS B and C subjects were required to have a Lower Extremity Motor Score (LEMS) of 5 or less points. - Clarified that, at study entry, American Spinal Injury Association Impairment Scale grade of A (AIS A) subjects with a level of injury at cervical level 4 must have at least 1 point of motor activity within the zone of partial preservation inclusive of cervical level 5 to thoracic level 1. - The previous version of the protocol the Spinal Cord Independence Measure, Version III (SCIM III) Self-Care subscale score to confirm the clinical meaningfulness of the primary endpoint. In order to accommodate the inclusion of AIS B and C subjects, the protocol was amended to use the total SCIM III score in this analysis. - Amended the supportive and exploratory efficacy endpoints to accommodate the inclusion of AIS B and C subjects. - Amended the lower age limit to 16 years and the upper age limit to 70 years for AIS B or C subjects. - Allowed sites outside the US and Canada to participate. - Specified that details of the method of imputation were to be included in the Statistical Analysis Plan (SAP).
02 June 2014	The overall reason for the amendment was to drop the requirement that AIS B and C subject must have a LEMS score of 5 or less points. - Amended the primary objective to be based on improvement in measures of overall functional independence based on the final mean total SCIM III. - Amended secondary objectives to include the final mean SCIM III Self-Care and Mobility subscale scores. - Added new secondary objectives related to Total Motor Score (TMS) and AIS grade. - Amended the definition of the Intent to Treat (ITT) population to include SCIM III, rather than International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) assessments. - Added an additional requirement to the ITT population that a subject must have received at least 7 doses of study drug. - Amended the sample size calculation to reflect changes in the primary endpoint. Sample size was changed from 164 subjects to 70 subjects. - Changed the number of sites to 70 with approximately 52 acute centers enrolling subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported